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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,694	11/01/2005	Tetsushi Taguchi	052203	7280

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,694	TAGUCHI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 2 April 2009 in which claims 1-3, 5-10 and 12-14 were cancelled, and claims 4 and 11 are amended to change the scope and breadth of the claims.

Claims 4 and 11 are pending in the instant application and are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/JP03/11669 filed on 1 November 2005 and claims priority to foreign application Japan 2002-265982 filed on 11 September 2002. A certified copy of the foreign priority document in Japanese has been received. No English translation has been provided.

Rejections Withdrawn

Applicant's amendment, filed 2 April 2009, with respect to the rejections of claims 4, 6, 7 and 11-14 under 35 USC § 112, first paragraph, for scope of enablement, has been fully considered and is persuasive because the claim as amended more specifically claims the subject matter disclosed and supported in Applicant's Specification.

Applicant's amendment, filed 2 April 2009, with respect to the rejections of claims 4, 6, 7 and 14 under 35 USC § 102(b) as being anticipated by Nagura *et al.*, has been fully considered and is persuasive because Nagura *et al.* do not specifically teach the

limitations of the instant claim wherein the high moleculare weight compound is collagen.

In view of the cancellation of claims 1-3, 5-10 and 12-14, all rejections made with respect to claims 1-3, 5-10 and 12-14 in the previous Office Action are withdrawn.

These rejections have been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 2 April 2009, wherein the limitations in pending claims 4 and 11 as amended now have been changed. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 28 January 2009, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section [0001]

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (machine translation, of record).

Nagura *et al.* disclose a biodegradable gelatin gel (paragraph 0002) that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages. Polycarboxylic acids included in the invention are, but not limited to, malonic acid, fumaric acid, succinic acid, adipic acid, citric acid, tartaric acid and malic acid. The gelatin gel is warm water-proof (paragraphs 004 and 0005) and is considered a biodegradable biomaterial that can be used as an artificial skin, wound dressing material, and a cell culture based material (paragraph 0018).

Although the invention of Nagura *et al.* is directed to gelatin gels useful as biomaterials, Nagura *et al.* further teach that water-soluble proteins such as water-soluble polysaccharides (such as chitosan, alginic acid and chondroitin sulfate) and collagen have been used as a biodegradable polymer gel film for cell adhesion (paragraph 0002). Moreover, much research has been made with collagen as biocompatible materials, such as an artificial skin substrate since it excels in biocompatibility as compared to gelatin (paragraph 0002).

Applicants are requested to note that since claim 4 is directed to a crosslinked high-molecular weight product, the recitation "obtained by modifying at least one carboxyl group of malic acid, oxalacetic acid, citric acid, or *cis*-aconitic acid with n-hydroxysuccinimide or N-hydroxysulfosuccinimide" is not a determination of patentability, so long as the product is the same. See MPEP § 2113.

The following is a quotation from MPEP § 2113:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Thus, one of ordinary skill in the art would have been motivated to substitute collagen in place of gelatin, in the method disclosed by Nagura *et al.* of a gelatin gel obtained by crosslinking a polycarboxylic acid, such as citric acid, with gelatin, in order to receive the expected benefit, as suggested by Nagura *et al.* that collagen excels in biocompatibility as compared to gelatin (paragraph 0002) and that the disclosed method of crosslinking a protein with a polycarboxylic acid produces a gel that is warm water-proof in nature (paragraphs 0004 and 0005).

[Section 0002]

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (of record) in view of Hermanson (chapter 3, entitled “Zero-Length Cross-Linkers", of record).

The teachings of Nagura *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

Nagura *et al.* do not teach polycarboxylic acids that are modified in at least one carboxyl group with N-hydroxysuccinimide or N-hydroxysulfosuccinimide.

Hermanson teaches zero-length crosslinkers that mediate the conjugation of two molecules by forming a bond containing no additional atoms. Zero-length crosslinking agents eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances (p. 169, paragraph 1). Carbodiimides, such as EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), are the most popular type of zero-length crosslinkers in use, being

efficient in forming conjugates between two protein molecules, between a peptide and a protein, between oligonucleotides and proteins, or any combination of these with small molecules (p. 169, last paragraph). N-hydroxysulfosuccinimide (sulfo-NHS) are hydrophilic active groups that react rapidly with amines on target molecules (p. 173, first full paragraph). Figure 108 provides a schematic of the reaction (p. 175). In the presence of EDC, sulfo-NHS modifies the carboxylic acid group of a molecule/protein to form a sulfo-NHS activated intermediate. In the presence of amine nucleophiles that can attack at the carbonyl group of the NHS-ester, the sulfo-NHS group rapidly leaves, creating a stable amide linkage with the amine (p. 173, first full paragraph). The advantage of adding sulfo-NHS to EDC reactions is to increase the stability of the active intermediate, which ultimately reacts with the attacking amine (p. 173, second full paragraph). EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, last paragraph).

A general protocol for the conjugation of a protein to a molecule (i.e. small molecule, peptide, another protein, etc.) is provided (p. 174-176). The protein to be modified is dissolved in 0.1 M sodium phosphate, pH 7.4 at a concentration of 1-10 mg/mL (p. 174, step 1). The molecule to be coupled is also dissolved in 0.1 M sodium phosphate, pH 7.4 (p. 175, step 2) and then added to a solution of the protein in at least a 10-fold molar excess over the amount of protein present (particular important when the conjugation is to a small molecule) (p. 175, step 3). EDC is then added to the protein/molecule solution to obtain a 10-fold molar excess of EDC to the protein (p. 175,

step 4). Alternatively, a 0.05-0.1 M EDC concentration would also work well. Sulfo-NHS, at a final concentration of 5 mM, is then added to the reaction (p. 175, step 4) which is allowed to proceed for 2 h at room temperature (p. 176, step 5) before purification of the conjugate by gel filtration or dialysis (p. 176, step 6).

It is noted that Hermanson does not explicitly teach the reaction conditions as indicated in the limitations of claim 11. However, it is considered well within the capabilities of one of ordinary skill in the art to optimize the reaction conditions to provide optimal conditions for the conjugation reaction. See below for recitation of section from MPEP § 2144.05. Furthermore, the protocol as disclosed by Hermanson provides for a range of workable conditions.

The following is a recitation from MPEP § 2144.05:

> A. Optimization Within Prior Art Conditions or Through Routine Experimentation
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning a biodegradable gelatin gel that is warm-water proof and obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages, with the teachings of Hermanson, regarding the mediation of the conjugation between a protein and a molecule with sufo-NHS/EDC. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that zero-length crosslinking agents (such as sulfo-NHS and EDC) eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct

linkage between the two substances (p. 169, paragraph 1). Moreover, Hermanson further teaches that EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation over that obtained solely with EDC (p. 173, last paragraph). Additionally, one of ordinary skill in the art would have been motivated to substitute collagen in place of gelatin, in the method disclosed by Nagura *et al.* of a gelatin gel obtained by crosslinking a polycarboxylic acid, such as citric acid, with gelatin, in order to receive the expected benefit, as suggested by Nagura *et al.* that collagen excels in biocompatibility as compared to gelatin (paragraph 0002) and that the disclosed method of crosslinking a protein with a polycarboxylic acid produces a gel that is warm water-proof in nature (paragraphs 0004 and 0005).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 2 April 2009 with respect to the rejection of claim 11 made under 35 USC § 103(a) as being unpatentable over Nagura *et al.* and Hermanson, have been fully considered but they are not persuasive.

Applicant argues that Nagura *et al.* do not teach any application using collagen, nor does the reference disclose any working examples using collagen. This argument is not persuasive because Nagura *et al.* teach that a gelatin gel crosslinked with polycarboxylic acid produces a gel that is warm water-proof in nature, and further teach that collagen excels in biocompatibility compared to gelatin. Thus, one of ordinary skill

in the art would have been motivated to modify the gelatin gel, and replace gelatin with collagen, to obtain a gel that is warm water-proof in nature. With regards to Hermanson, one would have been motivated to combine the teachings and use the disclosed methods of protein conjugation, in order to receive the expected benefit, as suggested by Hermanson, that zero-length crosslinking agents (such as sulfo-NHS and EDC) eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 4 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of co-pending U.S. application no. 10/543156.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a two-component bio-degradable/absorbable adhesive medical material comprising a bonding component composed of a solution containing a biodegradable polymer, and a hardening component composed of a derivative of a di- or tri-carboxylic acid of the citric acid cycle wherein at least one carboxyl group of the carboxylic acid is modified with an electron-attracting group. The electron-attracting group is one or a combination selected from the group consisting of a succinimidyl group, a sulfosuccinimidyl group, a maleimidyl group, a phthalimidyl group, an imidazolyl group, a nitrophenyl group and a tresyl group, and derivatives thereof. The biodegradable polymer is one or a combination of two or more selected from the group consisting of collagen, atelocollagen, alkali-solubilized collagen, gelatin, keratin, albumin, globulin, fibrinogen, glycosaminoglycan, chitin, chitosan, polyamino acid and polyalcohol, and derivatives thereof.

The claims of the instant application are drawn to a crosslinked high-molecular weight product obtained by crosslinking a high molecular weight compound with a biological low molecular weight compound, wherein the high molecular weight compound is collagen and the biological low molecular weight compound is obtained by modifying at least one carboxyl group of malic acid, oxalacetic acid, citric acid, or *cis*-aconitic acid with N-hydroxysuccinimide or N-hydroxysulfosuccinimide. It is general knowledge that N-hydroxysuccinimide and N-hydroxysulfosuccinimide are derivatives of succinimides and sulfosuccinimides.

Thus, the instant claim 4 is seen to be obvious over claims 1-3 of co-pending U.S. application no. 10/543156.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
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